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The Digital Twin Brain: A Bridge between Biological and Artificial Intelligence

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In recent years, advances in neuroscience and artificial intelligence have paved the way for unprecedented opportunities to understand the complexity of the brain and its emulation using computational systems. Cutting-edge advancements in neuroscience research have revealed the intricate relationship between brain structure and function, and the success of artificial neural networks has highlighted the importance of network architecture. It is now time to bring these together to better understand how intelligence emerges from the multiscale repositories in the brain. In this article, we propose the Digital Twin Brain (DTB)—a transformative platform that bridges the gap between biological and artificial intelligence. It comprises three core elements: the brain structure, which is fundamental to the twinning process, bottom-layer models for generating brain functions, and its wide spectrum of applications. Crucially, brain atlases provide a vital constraint that preserves the brain's network organization within the DTB. Furthermore, we highlight open questions that invite joint efforts from interdisciplinary fields and emphasize the far-reaching implications of the DTB. The DTB can offer unprecedented insights into the emergence of intelligence and neurological disorders, holds tremendous promise for advancing our understanding of both biological and artificial intelligence, and ultimately can propel the development of artificial general intelligence and facilitate precision mental healthcare.

Introduction

Demystifying the principles that account for intelligent human behaviors, such as recognizing faces and making decisions, has attracted huge interdisciplinary efforts and is the driving force behind the boom in artificial intelligence. The closer we approach the intrinsic nature of intelligence, the higher the possibility of mastering its emergence.

The multiscale characteristics of the human brain are being identified to explain the remarkable neurobiological basis underlying intelligent abilities. Even at the microscopic scale, the neuroanatomical characteristics of neurons have been linked to intelligence quotients [1]. With the development of neuroimaging techniques that provide in vivo observations of brain-wide morphological structures and functional activities, various brain regions have been found to correlate with general intelligence [2,3]. Further evidence suggests that human intelligence may emerge from distributed brain activity, emphasizing the integration of information processing across brain regions [4–6]. Moreover, the interaction/causality between brain regions during specific tasks is being explored to explain how the brain is involved in intelligent behaviors [7–9]. These neuroscientific findings systematically provide multiperspective biological priors of intelligent behaviors by studying the brain along with its network organization, i.e., simultaneously perceiving the effects of brain regions and their interactions. This is also consistent with brain organization, which can be empirically represented as structured networks [10]. Therefore, to understand intelligent behaviors conceived in the human brain by mathematically modeling brain activity, a systematic repository of the multiscale brain network architecture would be very useful for pushing the biological boundary of an established model.

Specifically, our point is supported by the great success of artificial neural networks in achieving human-like intelligent behaviors, although they lack biological realism. In particular, with unprecedented advances in the computing power of graphics processing units (GPUs), highly parallelizable GPU-enabled algorithms have accelerated the proliferation of deep learning techniques [11], which have revolutionized almost every field of research by way of artificial intelligence. We have recently witnessed excellent success of artificial neural networks in natural language processing tasks by OpenAI's ChatGPT [12] and computer vision tasks by MetaAI's segment anything model (SAM) [13]. The core idea underpinning these booms, the

artificial neural network, was first proposed almost 80 years ago by McCulloch and Pitts [14]. As they described, artificial neural networks have two basic elements: nodes and connections between nodes, which facilitate computational information flow within the network and share a conceptually similar computational paradigm with the biological brain. Therefore, in addition to the rapid development of computing technologies, the current success of artificial intelligence emphasizes the importance of network architecture if our goal is to empower a model with intelligence.

Despite the increasing optimism that artificial intelligence will transcend biological intelligence in the near future [15], it must be acknowledged that many distinctions exist between these two types of intelligence. In specific scenarios, such as playing video games, artificial intelligence can achieve a substantially higher performance than biological intelligence by reinforced learning from human behavioral data [16]. However, mounting evidence has demonstrated that artificial intelligence is vulnerable when facing adversarial situations that biological intelligence can easily avoid [17]. More obviously, biological intelligence can perform actions that are much more generally intelligent than those of current artificial intelligence, such as flexibly shifting between tasks from different domains, because the latter is usually trained with specific parameters. One of the essential reasons for these differences is that we still know too little about the computational mechanisms of biological intelligence to design a more biologically plausible artificial intelligence. It remains unclear whether we should rely heavily on the mechanisms of biological intelligence to achieve artificial intelligence. If the target is accurate performance in specific tasks, such as recognizing human faces, the answer may be no. However, if the goal is to develop artificial general intelligence or to make artificial intelligence behave more like human intelligence, it is necessary to pay more attention to how the brain processes information. Therefore, to establish connections between biological and artificial intelligence, a shared platform is required. Fortunately, as described above, the structure of neural networks, which is based on nodes and connections, provides a common computational paradigm shared by biological and artificial intelligence. This means that accumulated and upcoming knowledge about biological intelligence can be transferred to artificial intelligence in the form of networks. However, how should we pursue this?

We propose that the Digital Twin Brain (DTB) can bridge the gap between biological and artificial intelligence in the form of brain networks. The digital twin concept was first proposed for the Apollo mission at the National Aeronautics and Space Administration (NASA) in the United States. Since then, manufacturing and healthcare have been using digital twins, i.e., mockups of physical objects created using real-time data, to test various what-if scenarios. A DTB could enable virtual experiments on biological intelligent behaviors and mental health care to increase our understanding of the underlying mechanisms. However, how the digital twin technology should be applied to simulate the brain, especially the functioning processes of the brain, is largely unknown. Recent evidence from multiple independent studies has demonstrated the feasibility of simulation at the whole-brain level. Especially, EBRAINS, which is supported by the EU-cofunded Human Brain Project, provided The Virtual Brain (TVB) platform to accelerate full brain network simulations [18,19]. However, without sufficient biological plausibility, they are more useful in the field of simulation rather than as a digital twin of the brain. Therefore, we emphasize three essential elements for establishing the DTB, from architecture to the emergence of functions (Fig. 1):

1. As a biologically realistic digital twin of the biological brain, the DTB must have an architecture that has a close correspondence with that of the biological brain and reflects its regional heterogeneity across the brain. Without biological realism, we can only model the brain fragmentarily rather than digitally twinning it. Therefore, to seamlessly integrate biological findings for scaffolding the DTB, a multimodal and multiscale brain atlas covering the brain network organization is desirable.
2. When the DTB has been established by following the architecture of the biological brain, it should be able to generate functional signals that are close as possible to those of the biological brain using newly developed algorithms. That is, the DTB should be trained using functional data collected from biological brains. The result will be functionally similar to the built-in mechanisms of the biological brain in a way that results in functional activity from a comparable fixed model structure.
3. The DTB should demonstrate its value in a broad range of ways, such as by improving our understanding of the computing principles of brain functions or facilitating precision medicine by supporting clinical decisions with

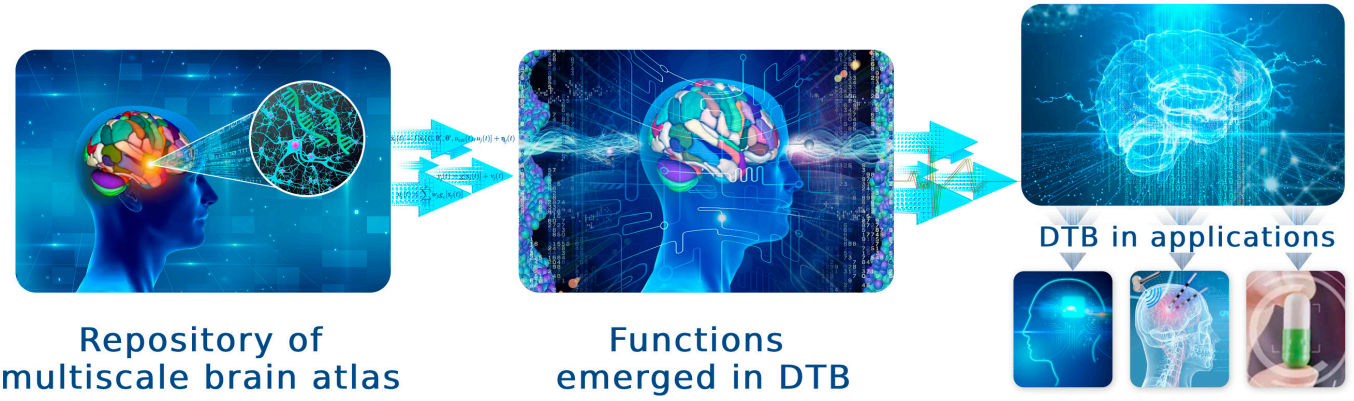

Fig. 1. Three elements in the DTB and the logical relationships between them.

more computational evidence. By testing the DTB in different types of applications, we can evaluate the advantages and disadvantages of the current twin model, which will drive the evolution of the DTB with respect to practical requirements. Finally, we may have the opportunity to understand how intelligence emerges from the network, how different types of brain diseases attack the network, and how the brain can leverage external stimuli to alleviate these attacks.

The DTB that we are proposing is far from the mind clones of science fiction. The establishment of the DTB is a learn-by-doing approach. By modeling brain activity with biological plausibility, we hope to increase our understanding of the mechanisms underlying biological computing details, which may be incorporated to advance the current form of artificial intelligence. The remainder of this paper is organized as follows. In the following three sections, we introduce the three key ingredients of the DTB: its structural basis, the three levels of models from micro single neurons to macro whole brains to generate brain functional signals, and the applications of the DTB in simulating and regulating brain dynamics. The final section discusses the challenges and potential of the DTB in opening new possibilities for future research.

Mapping the Human Brain: Brainnetome Atlas

Constructing brain atlases at different scales and modalities across different species is highly beneficial for the development of the DTB and for the computational modeling of neural systems. Brain atlases are comprehensive frameworks that encompass various aspects of the brain, including the demarcation of boundaries between different brain regions, characterization of their respective functions, identification of distinct neuronal cell types, and exploration of brain connectivity at different scales, ranging from the macro to meso to micro levels [20–25]. They can help us understand how brain regions are interconnected and how they interact at various levels of granularity. Such insights are crucial for modeling brain dynamics and simulating complex neural processes. Networks trained using biologically realistic connectivity often outperform those trained on random networks [26]. Integrating data from different imaging modalities can provide a comprehensive view of brain structure, connectivity, and activity. This multimodal approach enables us to capture complementary information about the brain, enhancing our ability to model and simulate neural activity with higher accuracy. Constructing brain atlases across different species, including humans and nonhuman animals, can further enable us to study evolutionary relationships and identify conserved brain regions and functional circuits [27]. This comparative approach aids in understanding the fundamental principles of brain organization and can provide insights into the neural mechanisms underlying cognition, behavior, and disease, thus providing important priors for building the DTB.

Cross-modal multiscale brain imaging is a fundamental technology underlying the development of brain atlases. Different imaging modalities capture diverse physical and chemical characteristics of brain structure and function. It is essential to integrate these modalities to obtain a comprehensive understanding of the brain as a unified entity that operates at multiple scales. Overcoming the challenges associated with integrating cross-modal information, bridging different scales, and accurately representing the spatiotemporal dynamics and intrinsic connections of brain structure and function is crucial for constructing brain atlases. Moreover, it is essential to establish a large-scale DTB. The purpose of building the DTB in the form of an architecture based on nodes and connections, which will be built on the foundation of a brain atlas, is to replicate the complex structural and functional characteristics of the human brain using a computational model. The integration of cross-modal, multiscale brain imaging techniques with the establishment of a large-scale DTB represents an important step toward elucidating the mysteries of the brain.

To this end, the team at the Institute of Automation of the Chinese Academy of Sciences proposed the further development of a human brain atlas called the Brainnetome Atlas [21]. This atlas incorporates multimodal brain connectivity information and encompasses 246 brain subregions, along with the structural and functional connectivity patterns between these subregions. Because it provides precise and objective localization of subregion boundaries and elucidates their functional implications, the Brainnetome Atlas constitutes a macroscale atlas of in vivo whole brain connectivity. In the future, this atlas will go multiscale and multifaceted, which will be an extensive and detailed mapping of the structure of the brain and its functional organization across multiple scales and dimensions. It will provide a comprehensive understanding of the brain by incorporating a wide range of information, including anatomical, physiological, molecular, and connectivity data obtained through various imaging techniques and experimental methodologies (Fig. 2). Using the Brainnetome Atlas, researchers can better understand the complexity of the brain and develop innovative approaches to challenges in brain science and related fields. More importantly, the Brainnetome Atlas provides a valuable resource for the development of DTB systems and novel design principles for brain-inspired artificial networks.

Brain Atlas-Constrained DTB Models

Computational models are critical components of the DTB that enable the replication of intricate characteristics of physiological signals, including raw neural activity and firing rate, functional magnetic resonance imaging (fMRI), electroencephalogram (EEG), and magnetoencephalography (MEG), while being constrained by brain structure. To model the brain comprehensively and accurately, it is essential to consider the microscopic level of individual neurons, the mesoscopic level of neuron populations, and the macroscopic level of the whole brain.

At the microscopic level, neuronal models capture the detailed behaviors and properties of individual neurons, such as their electrical activity, ion channel dynamics, and synaptic connectivity [28]. These models, including the integrate-and-fire model [29] and the Hodgkin–Huxley model [30], provide insights into the fundamental building blocks of brain function and allow us to study the intricate mechanisms underlying neuronal computations. The integrate-and-fire model, as well as its variants, has been widely used to explore brain dynamics at rest [31] and can be seen as a foundational model for artificial neural networks because it provides a basic framework for understanding how neurons integrate and transmit information [32].

At the mesoscopic level, neuron population models consider the collective behavior of groups of neurons that share common characteristics or are functionally connected [33]. These models capture the emergent properties and dynamics arising from interactions within and between populations of excitatory and inhibitory neurons. These models can be broadly categorized into two groups: biophysical and phenomenological. Biophysical models

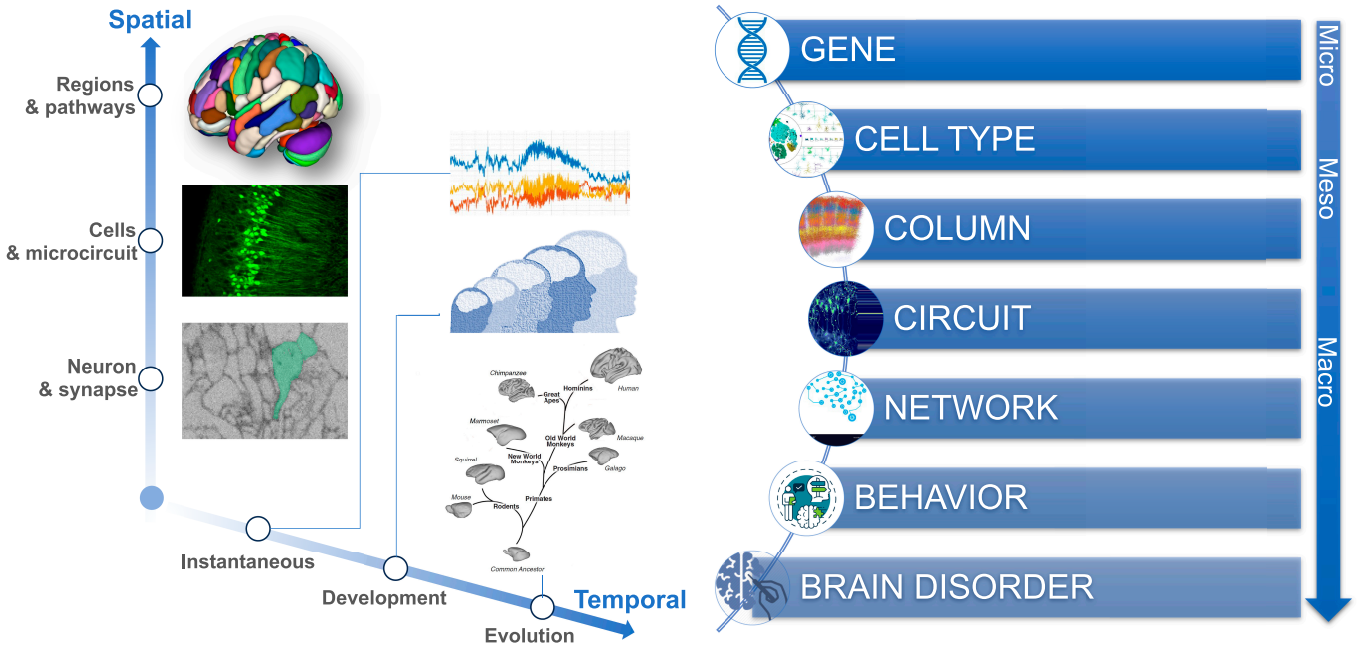

Fig. 2. Multiscale and multifaceted Brainnetome Atlas. The term "multiscale" indicates that the atlas will offer insights into the brain at different levels of resolution, ranging from macroscopic regions and networks to individual cells and molecular components. Moreover, it will provide a holistic understanding of the dynamics of the brain by considering temporal aspects, such as activity patterns, development, and evolution. The term "multifaceted" emphasizes that the atlas encompasses diverse aspects of brain organization and function. It will enable researchers to explore various facets of the brain, including its anatomy, connectivity patterns, activity dynamics, molecular composition, and behavior in healthy and disordered states.

describe the detailed biophysical properties and mechanisms of neuronal activity, whereas phenomenological models, such as the Kuramoto model, which characterizes the synchronized oscillatory behavior of neural populations [34], and the Hopf model, which generates periodic oscillations through a supercritical bifurcation [35], focus on capturing the overall patterns and dynamics of neural activity without explicitly modeling the underlying biophysical processes [36]. Examples of biophysical models include the Wilson–Cowan model, which characterizes the average firing rate of neuronal populations [37], a reduced spiking network developed by Wong and Wang [38], and a dynamic mean-field (DMF) model with local feedback inhibition regulating the firing rate to approximately 3 Hz for each local excitatory population by Deco et al. [39,40]. Combined with multimodal data, these models show how large-scale patterns of activity and information processing emerge from the collective behavior of neurons.

Finally, at the macroscopic level, whole-brain models integrate information from different brain regions and networks to capture the global dynamics and functional connectivity of the whole brain, which are constrained by brain structure. These models enable us to investigate how different brain regions interact and influence each other, leading to complex cognitive processes and behaviors. Moreover, whole-brain models are complex systems composed of multiple factors that interact and coevolve over time [41]. Each of these systems is a comprehensive framework that can be used to simulate the dynamic patterns of the brain and investigate the underlying mechanisms that drive the observed phenomena. For whole-brain modeling, model fitting is a crucial process of tuning parameters to improve accuracy, gain a deeper understanding of the underlying system, and make accurate predictions. Two fitting methods are commonly used: parameter space exploration and model inversion. The former explores all possible parameter combinations and selects the best fit [42]. The latter is a backward method that uses machine learning to infer the posterior distribution of model parameters from observed data [43,44]. Although either method can lead to accurate results, the types and ranges of the parameters should be chosen according to the specific context, as choosing requires making trade-offs between model complexity and accuracy. Various factors, including data preprocessing [45], the number of brain parcellations and their long- and/or short-range connections [46–48], and model paradigms [49], affect the results to some extent. Thus, there is no consensus on how to choose parameter configurations. One of the key advantages of whole-brain modeling is its ability to analyze and interpret model parameters in relation to real data, which produces insights into specific physiological phenomena [50]. In addition to serving as tools for studying brain function, whole-brain models are platforms for testing hypotheses and predicting the response of the system under different conditions. By adjusting the model parameters, the effects of specific interventions or perturbations can be explored. This could be particularly valuable for developing new therapies or treatments for brain disorders [51,52].

By considering these three levels of brain modeling, we gain a more comprehensive understanding of the complexity of the brain and the networked interactions that shape its functions. This multilevel approach allows us to bridge the gap between the microscopic details of neuronal activity and the macroscopic patterns of brain dynamics, ultimately advancing our knowledge of brain functions and their roles in various neurological and psychiatric disorders.

Modeling Brain Functions, Dysfunctions, and Interventions in the DTB

With the biological counterpart and bottom-layer models, many things can be done within the framework of the DTB,

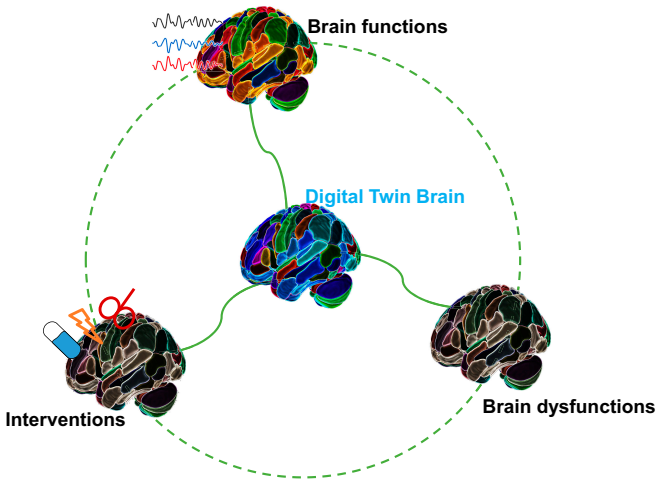

Fig. 3. Schematic diagram of modeling brain functions, dysfunctions, and interventions in the Digital Twin Brain (DTB). Using the DTB, we can model normal brain activity in resting states and simulate different types of cognitive tasks. Modeling brain dysfunctions is helpful for revealing the underlying neuropathology of brain diseases by comparing it to a healthy functioning brain. Different interventions, including deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and pharmacological interventions, can be modeled and utilized to modulate the brain dynamics from an undesirable (e.g., unhealthy) to a desirable (e.g., healthy) state.

including simulating how the brain works in resting and task states, modeling brain dysfunctions in brain disorders, and restoring brain dynamics from undesirable to target states. In this section, we review some application studies for the DTB (Fig. 3).

Modeling brain functions in the DTB

In the biological brain, different types of brain functions with specific spatiotemporal patterns are generated by a relatively stable neuroanatomical scaffold. However, the underlying mechanisms remain unclear. The difficulty lies in the lack of a quantitative method for measuring the functional computing mechanisms underlying different brain functions. By approaching brain-like functional signals, the DTB could provide a quantitative way to understand the mechanisms through which different brain functions emerge from a consistent structural organization.

By roughly allocating different types of neurons to large brain regions, researchers began to simulate human brain activity at the whole-brain level almost 15 years ago. For example, Izhikevich and Edelman [53,54] proposed a simplified spiking neuron model of the thalamo-cortical system that simulates 1 million multicompartmental spiking neurons of 22 basic types and almost half a billion synaptic connections. By offering a set of parameters, this model can reproduce known types of responses recorded in vitro in rats and help analyze the behavioral mechanisms of normal brain activity in humans. Similarly, based on the different functional roles of brain regions, Eliasmith et al. [55] designed the Semantic Pointer Architecture Unified Network (Spaun), a large neural network comprising 2.5 million spiking neurons, to recognize and switch between eight different tasks, including image recognition and serial working memory. The same research group developed the Spaun 2.0 model, which comprised approximately 6.6 million neurons and was capable of performing 12 different cognitive tasks [56]. Although the functional modules of the model primarily corresponded to specific brain regions, the creation of Spaun and its updated version demonstrated the feasibility of establishing models to conduct various tasks by following the organizational principles of the human brain. If the model could be improved biologically, such as by making the functional signals generated from the model more similar to those of the human brain, we could gain further understanding of how the brain functions by examining the parameter space of the model.

By modeling the functional dynamics of brain regions, several whole-brain models have been established to simulate resting-state functional connectivity at the macroscale [18,57,58]. Recently, Lu et al. [59] established an extremely large-scale whole-brain simulation using the leaky integrate-and-fire model as the basic computing unit. Specifically, this model comprised up to 86 billion neurons, close to the estimated number of total neurons in the human brain, and had 10 trillion synapses for spike communication, which could simulate brain functional activity both in the resting state and in vision and auditory tasks. However, it still has not closely touched on the ways in which biological information about brain regions could contribute to these models and how brain functions should be generated.

Clearly, to simulate brain function at the magnitude of a billion spiking neurons, the computing resource requirements are extremely high, e.g., 10,000 GPUs to implement simulations in the work mentioned above [59]. If more biological features, such as different axonal densities and mantle layer information, are added, the computational load will likely increase exponentially. Therefore, a balance between biological plausibility and computational possibility must be sought. Accurate biological information may help alleviate the computational load by merging similar neurons into cortical columns or refined brain regions. Thus, by using the accurate biological information in the Brainnetome Atlas, the DTB may be started at the macroscale level. As the Brainnetome Atlas progresses toward the microscale level, the DTB can be updated in a more biologically meaningful direction. Simultaneously, it is necessary to develop new models that efficiently represent biological features. Additionally, new neuromorphic computing hardware, such as the BrainScaleS system [60], the Pohoiki Springs system [61], and the Darwin Mouse computer [62], may contribute to accelerating and lowering the cost of the large-scale twinning process.

In addition to these studies on functional simulation at the whole-brain level, more studies have been conducted from the perspective of computational neuroscience to investigate the dynamic mechanism of brain functions based on local neural circuits. For example, the spiking circuit model has been applied to investigate the neuronal mechanism of decision-making [38,63,64] and the emergence of stable neuronal timescales to support working memory [65]. These recognized local circuits and dynamic principles provide a repository for simulating the local activity of specific brain regions when establishing the DTB for the corresponding tasks. However, more efforts are required to establish a series of methods that can efficiently interrelate these local circuits and fit them into the model.

Modeling brain dysfunctions in the DTB

Because they are affected by various factors including physiology, psychology, and social environment, the underlying pathogenic mechanisms of many psychiatric and neurological disorders remain elusive and require new techniques in addition to

experimental studies and theory. In recent years, computational models have provided a new perspective for the mechanistic analysis of brain functions and disorders [66], such as schizophrenia [67,68], brain tumors [69,70], and epilepsy [71]. The advantages of this research approach lie in the fact that these methods not only simulate bio-plausibly dynamic mechanisms of brain diseases at the neuronal scale, at the level of neural populations, and at the brain region level but also perform virtual surgical treatments that are impossible to perform in vivo owing to experimental or ethical limitations [72]. These methods provide powerful tools for studying brain diseases through the relationship between brain structure, function, and dynamics. Here, we provide an overview of some influential studies from the perspective of functional and structural abnormalities.

Research indicates that many mental and neurological diseases are related to connectivity imbalances. Changes in excitatory–inhibitory (E/I) balances within local microcircuits are believed to result in the altered functional networks observed in these diseases [73]. These changes can be simulated by biophysical models. For example, schizophrenia is often conceptualized as a disorder of altered brain connectivity [74] and is hypothesized to be associated with elevated E/I ratios in cortical microcircuits [75]. Yang et al. [68] utilized a DMF model to study the dynamics of brain networks as a function of local and global parameters and found that the empirically observed increases in voxel-wise variability and global signals in schizophrenia might arise from local recurrent self-coupling within nodes and long-range global coupling between nodes. The same group extended this line of research to simulate the impact of elevated E/I ratios on model-derived functional connectivity by altering key biological parameters [67]. This study revealed that the model predicted the hyperconnectivity of functional connectivity for elevated E/I ratios and showed that models that account for the heterogeneity of association and non-association cortical regions could better explain the spatial pattern of functional connectivity changes observed in neuroimaging data in schizophrenia. Benefiting from computational models, such disruption of macroscopic brain connectivity can be explained. In addition, research on brain dysfunction caused by E/I imbalances in local microcircuits has been widely applied to brain diseases, including Alzheimer's disease [76] and stroke [77].

Other brain diseases arise from disruptions in brain functional connectivity caused by alterations in structural networks, and their effects on brain activity can generally be investigated by the simulated lesioning (removing edges) or resecting (removing nodes) of specific brain structures [78]. Based on personalized structural connectivity, Aerts et al. [69,70] analyzed the impact of changing structural connectivity on a postoperative spatial function by using "virtual neurosurgery" for a tumor resection and found that this method improved the prediction of postoperative brain dynamics in patients with brain tumors. Similarly, to assess the effect of lesions on temporal dynamics, Wei et al. [79] simulated the lesions of specific nodes by regulating their connection strengths. This study revealed that lesion effects exhibited regional dependence and could be predicted by the anatomical hierarchy axis and specific measures of structural brain networks.

Epilepsy, a disease associated with both structural and dynamic changes in the brain, often manifests with symptoms that spread from an onset zone to other distal areas along white matter tracts [71,80]. Jirsa and colleagues [43,71,80,81] have conducted many leading studies on epilepsy from a macroscale perspective. They proposed a virtual epileptic patient (VEP) based on individual brain networks to simulate individual seizure propagation patterns [71]. In this model, whether each node is in the epileptogenic zone can be determined based on the excitability threshold. By comparing the predicted foci with clinical decisions, the VEP model demonstrated promising results in clinically useful estimations [82–84]. In addition to studies from a macroscale perspective, there are many other computational models of epilepsy, including those on a single-neuron scale [85].

Collectively, computational models have the potential to provide insights into the mechanisms underlying brain diseases and aid in the design of interventions. In addition to the abovementioned mean-field models, some single-neuron models also have a wide range of applications in brain diseases, such as in modeling striatal microcircuits based on single-compartment models with Hodgkin–Huxley-type dynamics to simulate the potential source of enhanced beta rhythms in Parkinson's disease (PD) [86]. Critically, applying anatomical connectivity as a structural scaffold requires authentic and reliable brain atlases. Incorporating prior knowledge of the brain, such as spatial heterogeneity/hierarchy characterized by intracortical myelin content [87], functional gradient [88], and gene expression profiles [89], into the computational model would aid research on the mechanisms of brain diseases. In addition, disease-specific models should be formed according to the specific etiology of the disease because different brain disorders have different pathologies [72]. These models would also benefit from iterative updating along with increased information on brain dysfunctions.

Modeling interventions of brain diseases in the DTB

The goal of modulating brain dynamics is to predict the outcomes of external interventions, either physical or chemical, and to design new therapeutic strategies for brain diseases. In the current era of the rapid development of intelligent computing, modeling interventions of brain diseases in the DTB has the potential to provide cost-effective evaluations for clinical diagnosis and treatment before beginning clinical trials. Currently, intervention techniques, including invasive deep brain stimulation (DBS), noninvasive brain stimulation (NIBS), and pharmacological intervention, are being widely modeled to study the resulting brain dynamics at multiple topological scales from a phenomenological or predictive perspective [52,90].

Modeling invasive neuromodulation: DBS

DBS is a typical invasive technique that induces modulation by applying high-frequency electrical stimulation to a specific brain area. It is an effective physiotherapeutic method for neurological and psychiatric disorders, such as PD [91] and treatment-resistant depression [92,93].

Using PD as a case study for the application of DBS, attempts have been made to model neuronal dynamics in PD, from the microscopic scale of single neurons to the macroscopic scale of whole-brain networks [94]. Biophysical modeling of PD has mainly focused on the cortex–thalamus–basal ganglia circuit through direct, indirect, and hyper-direct pathways of projections from the cortex to subcortical nuclei, and the models have included the conductivity-based Hodgkin–Huxley model, the simplified spike-based Izhikevich model, and the reduced mean-field model [95]. Key clinical biomarkers of PD, such as pathological electrophysiological oscillatory (e.g., beta band) activity, have been reproduced to reveal the potential

mechanisms of the action of DBS [96] and further to identify the optimal stimulus parameters to restore normal neuronal dynamics at the right stimulation frequency [97] and time [98].

In most thalamo-cortical microcircuit models, the entire cortex is modeled as a single spiking network node, and simple synaptic connections that generate neural activity are modeled. However, neuromodulation-induced changes in cognition do not arise directly from the modulation of individual neurons but from neural populations and circuits at the mesoscopic level [99]. In addition, the highly networked structure of the brain implies that localized perturbations not only yield localized effects but also induce indirect effects that propagate along neural pathways [100], making it more appropriate to simulate neuromodulation at the meso and macroscopic scales. Therefore, a whole-brain macroscopic perspective is required for understanding the networked modulating effects of DBS. Recently, a large-scale network model was proposed to bridge the microscale of single spiking neurons and whole-brain signals in a multiscale model to perform virtual stimulations and forecast the outcome of DBS for PD patients [101]. At the macroscopic scale, the whole-brain network model has been used to uncover the biophysical mechanism and explore stimulation targets for major depression [102] or combined with network control theory to design an optimal control strategy [103,104]. However, in most computational DBS studies, the electric field potential (voltage distribution) induced by stimulation was not considered. Such studies are useful but somewhat unrealistic. Usually, the stimulus-induced potential field is forwardly calculated using a quasi-static approximation and the finite-element method [105]. Recently, progress has been made in developing a large-scale computational model that considers the electric field potential induced by DBS at the whole-brain level, showing its capacity and potential for identifying stimulation sites and parameters for treatment-resistant depression [106]. However, the computational integration of DBS-induced electric fields and large-scale models needs to be further developed.

Modeling noninvasive neuromodulation: tES and TMS

Noninvasive brain (electrical) stimulations (NIBS) modulate brain functions by applying an electrical current to the scalp. These electrical stimulations include the widely used transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), which includes transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) [90]. The main difference between TMS and tES is that TMS generates a magnetic field that induces an electric field that activates neurons, whereas tES modulates the neural activity without inducing action potentials using low-voltage current [105,107].

Computational modeling of NIBS is more complicated than DBS modeling because NIBS involves indirect neuromodulation [108]. Usually, the stimulus-induced potential field of NIBS is calculated with high-resolution head models and then used as input to cortical neurons that simulate neural responses. This type of integrative modeling has been studied at the microscopic level of multicompartmental neurons for computational estimations of TMS- and tES-induced neuronal responses [105]. However, at the mesoscopic and macroscopic levels, the interaction of external fields with neuronal models has rarely been considered in modeling. In most biophysical modeling of NIBS, TMS- and tES-induced neural responses are phenomenologically modeled to reproduce experimental data and then provide mechanistic explanations, such as how tACS entrains alpha oscillation in the thalamo-cortical system [109] and how tDCS [110] and tACS [111] influence the spatiotemporal dynamics of cortical network dynamics, using spiking neuron models without considering an external stimulus-induced potential field. Similarly, many studies have focused on modeling the motor cortex for the reproduction of indirect responses [112] and motor-evoked potentials [113,114] following TMS. The underlying mechanism of TMS-induced neural plasticity was also computationally explained by neural population models based on neural field theory [115,116] while neglecting the impact of an externally applied field.

NIBS typically stimulates a few square centimeters of cortex; thus, it is more appropriate to simulate the collective dynamics of neurons at the macroscopic scale [116]. Meanwhile, the current or voltage distribution induced by an externally applied field, identified through forward calculation, is critical for the biophysically plausible modeling of NIBS at the macroscopic scale. One study applied the tDCS-induced current density distribution in a whole-brain model to investigate how tDCS effectively changed the spatiotemporal dynamics in resting-state functional connectivity [117], making a step forward toward biophysically realistic modeling. Despite progress similar to that in DBS studies, the incorporation of neuronal ensemble dynamics and an externally applied field is still a critical issue to be addressed for the predictive large-scale modeling of NIBS.

Modeling pharmacological intervention

As previously mentioned, many neuropsychiatric diseases are hypothesized to involve an E/I imbalance. Pharmaceuticals are designed to restore the E/I balance in the brain by exciting or inhibiting the binding of related neurotransmitter receptors. For example, the 5-hydroxytryptamine psychedelic can bind with serotonin receptors to generate modulating currents, and ketamine and other *N*-methyl-D-aspartate (NMDA) receptor antagonists can directly bind to NMDA receptors to affect excitatory neural currents. Modern biotechnology usually focuses on understanding the metabolic pathways related to disease states and manipulating these pathways using molecular biology or biochemistry. In contrast, the DTB is designed to simulate changes in brain states caused by different neurotransmitters or neurotransmitter receptor alterations to aid computational investigation into which and how substances regulate brain functions; the focus will be especially on neuropsychiatric disorders, such as depression [118] and Alzheimer's disease [119].

Many studies have explored the quantitative relationship between neurotransmitter concentration and the modulating current in vivo [120]. There are also models that describe the effects of neurotransmitters, such as dopamine and τ protein at different concentrations, on the E/I balance [41,121,122]. However, studies that directly investigate the impact of pharmaceuticals on the E/I balance at the macroscale are still in their infancy. We list some related studies in Table and introduce a dynamic coupling model for psilocybin to demonstrate the potential of pharmacological interventions using the DTB. Psilocybin, a type of 5-hydroxytryptamine psychedelic, is an agonist of the serotonin 5-hydroxytryptamine 2A (5-HT_{2A}) receptor. Psychotherapy assisted by this type of psychedelic has demonstrated substantial positive relief of anxiety and depressive symptoms in patients with psychological and social distress [123–126]. To explain the functional effects of serotoninergic 5-HT_{2A} receptor stimulation with psilocybin in healthy humans, Deco and colleagues [118] simulated the release-and-reuptake

Table. List of computational studies on pharmacological interventions.

References	Substance	Model	Model fit to	Parcellation
Deco et al. [118]	Psilocybin	Dynamic mean-field model	Kullback–Leibler distance	AAL (90)
Deco et al. [153]	Lysergic acid diethylamide (LSD)	Dynamic mean-field model	BOLD FC	AAL (90)
Jobst et al. [154]	LSD	Hopf model	BOLD FC	AAL (90)
Ruffini et al. [155]	LSD	Ising model	Ising temperature etc.	AAL (90)
Stefanovski et al. [119]	NMDA receptor antagonist	Jansen–Rit model	Neural activity EEG	Glasser (360)
Coronel-Oliveros et al. [156]	Nicotine	Jansen–Rit model	Functional connectivity dynamics	AAL (90)
Coronel-Oliveros et al. [157]	Nicotine	Jansen–Rit model	Functional connectivity dynamics	Schaefe (100)
Coronel-Oliveros et al. [158]	Noradrenaline	Jansen–Rit model	EEG	AAL (90)
Deco and Thiele [159]	Acetylcholine	Leaky integrate-and-fire model	Neural activity	/
Sajedin et al. [160]	Acetylcholine	Leaky integrate-and-fire model	Neural activity	/

dynamics of the 5-HT_{2A} neurotransmitter system by inducing the 5-HT_{2A} receptor density and coupled it with the neuronal activity at the whole-brain scale. This mutual coupling model provides new insights into how psilocybin acts on the serotonin system and further modulates brain activity. Thus, it shows considerable promise as a therapeutic intervention for depression. In short, the impact of chemical substances on neural activity can be predicted prior to clinical trials, which helps in developing drugs, designing pharmacological interventions, and providing guidance for brain diseases. Using the explanatory and predictive power of the DTB, we can simulate the rebalancing of human brain activity in silico.

Perspectives

The DTB opens a new avenue for elucidating the basic principles of the brain and for revealing the complex neural mechanisms behind brain functions and dysfunctions, thus establishing a new paradigm of integration between the understanding, simulating, and controlling of the brain, and more importantly, bridging the gap between biological and artificial intelligence. As discussed previously, notable progress has been made so far. However, it is still in its infancy, and many open questions remain. Here, we present some representative ones that are essential for the study of DTB.

Achieving a digital twin of the biological brain based on a cross-modal, multiscale brain atlas

The core idea lies in how to draw inspiration from and extract the framework and dynamic information provided by the brain atlas and develop relevant modeling methods to make a digital twin of the brain. This can be achieved from two perspectives. First, the development of a brain atlas provides a real data foundation for establishing a digital twin of the biological brain, including a reference of structures and functions at different spatial and temporal scales. This ensures that the digital twin of the brain will approximate the real neural system, not only in terms of structural resemblance but also in terms of functional similarity. Second, to improve and validate cognitive computing models, the brain atlas will provide multi-omics, multiscale structural descriptions, and dynamic activity information. This includes genetic information related to the genome, which is currently lacking in artificial intelligence models, the coupling and generative relationships between brain structure and function, knowledge of conservation and variation in the evolution of the nervous system, and the low-dimensional and nonlinear basic laws of the nervous system in terms of structure and function.

The knowledge provided by a brain atlas and the latest biological discoveries will continuously improve the digital twinning of the brain, making it increasingly realistic, as recent progress that has already been made in simulations informed by brain structure [87], function [88], and genetic profiles [89]. These studies have shown that the multiscale and heterogeneous organization of the biological brain is crucial for building a bio-plausible DTB and understanding the structure–function–dynamics relationships of real brains, thus linking micro-meso-macroscopic phenomena with behavior. Using multimodal brain imaging and multi-omics data, relating macroscopic phenomena and behaviors to their mesoscopic circuits and microscopic neurons or synapses is critically vital for future DTB research. Ultimately, this advancement will drive the realization of general artificial intelligence and understanding of the source of intelligence.

How to build a more realistic and reliable model

A more realistic model of the brain is crucial for advancing knowledge and applications in neuroscience. Such a model would enable us to delve deeper into the complexities of brain function, make more accurate predictions, and improve clinical interventions. Although computational models of the

brain have made remarkable progress in various applications, several challenges and constraints remain unaddressed:

- When modeling a single neuron, it is crucial to consider how to effectively capture the spatiotemporal characteristics beyond simply describing the electrical activity of dendrites [32]. Neurons exhibit intricate branch structures and complex spatial topologies. Existing models often focus on either depicting synaptic membrane potentials, capturing only temporal dynamics, or simplifying neurons as one-dimensional entities, as in the case of cable equations [127]. To enhance our understanding of information processing and propagation in the brain, it is crucial to advance modeling approaches that embrace multidimensional space. By incorporating multidimensional space modeling, we can capture the intricate shapes and connectivity patterns of neurons more accurately. This, in turn, enables us to gain deeper insights into neural phenomena, such as synchronization, oscillation, and network dynamics. A comprehensive exploration of multidimensional space modeling will contribute to advancements in neuroscience research and our understanding of the complexities of neural systems.
- When modeling neuron populations, a critical issue is the effective integration of diverse structural components to enhance neuronal activity and capture cross-scale interactions. This includes the incorporation of factors such as connectivity [31], geometry [128], and microstructure [129]. Current cross-scale integration models have made notable advancements in nesting micro-meso-macro layers [118]. However, because their focus is often limited to individual or multiple microscopic attributes [41], they fail to capture the full mutual influence and interactions of the different layers. To advance these models, a critical next step is the comprehensive integration of various microscopic attributes, including genetic factors, receptor dynamics, and myelin integrity, with particular emphasis on characterizing their interactions. By incorporating these diverse elements into the models, we can achieve a more comprehensive understanding of the complex interactions and dynamics within the neural system, and gain insights into brain function and information processing at multiple scales.
- When modeling the whole brain, verifying the accuracy and reliability of the model is key to the transition from theory to application [83]. Although these models aim to simulate real-world dynamics as closely as possible, it is important to remember that simply fitting the data well does not guarantee the usefulness or validity of the model. Although notable progress has been made in whole-brain simulation, which has primarily focused on mechanistic explanations and simulation regulation, the transition to practical applications necessitates validation with real data. The next critical step involves the rigorous testing and validation of these simulations using empirical data and experimental findings. Such testing and validation will ensure the accuracy, reliability, and relevance of the models in real-world scenarios, enabling their successful integration into practical applications such as clinical diagnosis, treatment planning, and personalized medicine. By bridging the gap between theory and application, whole-brain simulation can revolutionize neuroscience research and improve our understanding and management of brain-related disorders.

How can we imbue the DTB with multimodal human-like intelligence?

By using brainnetome priors that emphasize the integration of the multiscale network-based biological priors of human brain organization, the new architecture of the DTB could be designed with greater biological fidelity. However, great challenges still exist in combining or hybridizing human intelligence and the DTB, ranging from low-level perceptual functions (e.g., visual and auditory processing) to high-level cognitive functions (e.g., language and memory).

The most obvious difference between the human brain and the DTB may be the inputs. The human brain can easily process visual, acoustic, tactile, and olfactory inputs. Without comparable inputs, subsequent processing by the DTB may not be comparable to the human brain functioning with multimodal inputs. Therefore, finding a way for the DTB to receive multimodal and human-comparable inputs is the first challenge in approaching human intelligence. One possible method is to use current deep-learning techniques to generate human-comparable inputs. Accumulated evidence has demonstrated that the activity of convolutional neural networks resembles that of the human visual cortex when it is processing visual inputs [130,131]. Similarly, convolutional neural networks have demonstrated correspondence with the functional activity of the human brain when encountering the same acoustic stimuli [132–134]. Therefore, pretrained neural networks may be adopted to provide modal-specific inputs to the DTB. However, further efforts are required to validate and harmonize these inputs.

Another key property of human intelligence, and one that presents a great challenge for artificial general intelligence, is functional flexibility. Currently, one popular strategy for achieving artificial general intelligence is the development of large artificial intelligence models, such as large language models, that consist of more than 100 trillion parameters. By increasing the parameter space, large models may be able to achieve state-of-the-art flexibility in specific task domains. However, the human brain does not achieve its functional flexibility by having specific large models for specific task domains. By contrast, in a diverse task context, the human brain can respond smoothly to multiple inputs using the same biological system. Therefore, building a collection of small but efficient models may be a more rewarding path to functional flexibility and could reveal evidence for whether or to what extent intelligence comes from brain organization. A promising approach may be to consider the neuromodulatory system in the subcortical nuclei, which relays and gates the flow of sensory information to the cortex for adaptation to diverse inputs. The connectivity patterns between the subcortical nuclei and cortex can be learned, and may further be adopted to design the gating components of the DTB for conducting various tasks. Therefore, a plethora of further research is required.

Ultimately, the goal is to have not just an intelligent supercomputer developed from the brain-inspired artificial neural network but also an enhanced understanding of the mechanism of human intelligence through brain-organization-aware models. It would then be a virtuous cycle to decipher human intelligence by modeling it using known brain priors and then further refining the model using newly learned insights.

DTB in brain diseases: From in silico to clinic

Studies on brain diseases can benefit from the DTB by analyzing the mechanisms underlying the disease and simulating clinical surgery, brain stimulation, drug therapy, etc. Currently, the neuropathologies of many brain diseases are only partially understood, but new findings keep popping up [135–141]. This will make the DTB an invaluable tool for exploration and validation. More promisingly, the DTB could be used to investigate different hypotheses regarding brain dysfunctions. Because we can also manipulate brain activity in silico in unprecedentedly rich ways that are not feasible in real human brains, we may achieve results of great scientific and clinical importance.

The DTB has the potential to provide a new paradigm for neuromodulation by virtually simulating both physical and chemical interventions addressing changes in brain dynamics. Taking the treatment of major depression as an example, a major challenge of traditional treatment methods, including brain stimulations (e.g., DBS) and pharmacological treatments (e.g., ketamine), is to test the effectiveness of these treatment modalities via preclinical experiments in humans [142], which are usually not allowed. Using the DTB, potential treatments for major depression can be tested harmlessly and effectively from various perspectives. Such testing could include safe drug dosages of ketamine and optimal stimulation targets of TMS or DBS. Moreover, most current medicines targeting neural systems have limited efficacy despite a long development cycle. The DTB has the potential for use in drug discovery, for example, by simulating the possible effects and side effects of newly developed substances to screen for potential drugs. By using model support from the DTB, it might be possible to guide and greatly shorten the process of drug discovery, thereby enabling more efficient drug development. To achieve this, it is necessary to properly simulate the way that these chemical substances act on neural systems and how neurochemical systems interplay. Linking microscale molecular dynamics or pharmacodynamics and system-level brain dynamics may be a possible way of modeling pharmacological interventions with biochemical plausibility. This new paradigm can also be similarly applied to brain stimulations, and stimulation configurations, e.g., optimal targeted brain area and stimulation frequency, can be explored and assessed in the DTB. Nevertheless, as mentioned previously, how to integrate brain dynamics with an externally applied field is still a critical issue for both DBS and NIBS and needs to be addressed before biophysically realistic neurostimulations can be obtained.

Individual differences exist, and diagnosis and treatment are made on a case-by-case basis in clinical contexts. In particular, it is quite likely that specific brain areas or circuits are modulated during specific states for different patients under neurostimulation. Applying the DTB has the potential to digitally facilitate precision medicine for brain diseases; however, this requires modeling at the individual level, while current studies are mostly group-wise or use individual features (e.g., structural connectivity) that have been extracted from a group template. Thus, it is necessary to develop an individualized DTB that enables personalized virtual therapies. But how? An individualized brain atlas may provide the basis for adapting the DTB at the individual level. Another possible approach to individualization is to pretrain the DTB on a large sample of healthy controls and then fine-tune it using the personalized data of a specific patient.

In general, efforts are still underway to advance the study of brain diseases in the DTB from phenomenological to predictive modeling, and further, from in silico to clinical settings. The study of brain diseases using the DTB will require applying information from cross-modal and multiscale brain atlases, gaining new knowledge about brain dysfunctions, and designing bio-plausible assumption-based models. This is a challenging process but will greatly benefit the design of personalized, efficient, and effective treatment strategies for a variety of brain diseases. Meanwhile, we should always be aware that these computational frameworks must be carefully validated with neurobiological experiments and empirical data before the DTB is used in clinical applications.

Key challenges of the DTB platform

Cross-modal and multiscale DTB simulations cannot be performed without the support of an efficient simulation platform. Building such a platform involves multiple technical fields, including numerical simulation and modeling, neuroinformatics, neuronal and neural network modeling, brain dynamics modeling, and brain atlases, as well as front-end and back-end engineering development based on different technology stacks, algorithm optimization, multicore parallelism, and hardware acceleration using GPUs. A few neuroinformatic platforms exist, covering the brain from a single neuron to the whole brain. These include Neuron [143], Brain 2 [144], BrainCog [145], BrainPy [146], TVB [18,147], and Neurolib [148]. However, most of them suffer from the following limitations: (a) Relevant atlases either are not integrated into existing platforms or are available in limited quantities. (b) Cross-modal multiscale simulation capabilities are limited. (c) They have low simulation efficiency owing to poor code optimization or inadequate support for hardware acceleration. (d) They are not sufficiently user-friendly because they require users to write code. (e) They lack modules for quickly and easily visualizing and analyzing the simulation processes and results. In brief, current neuroinformatic platforms cannot readily support multiscale cross-modal DTB modeling and simulations based on a brain atlas. Therefore, it is crucial to develop an open-source, efficient, flexible, and user-friendly brain atlas-constrained DTB platform that supports multiscale and multimodal modeling.

In conclusion, we here outlined a blueprint of the closed-loop DTB from our perspectives by emphasizing the interaction of three cores of the DTB (Fig. 4). With the multiscale

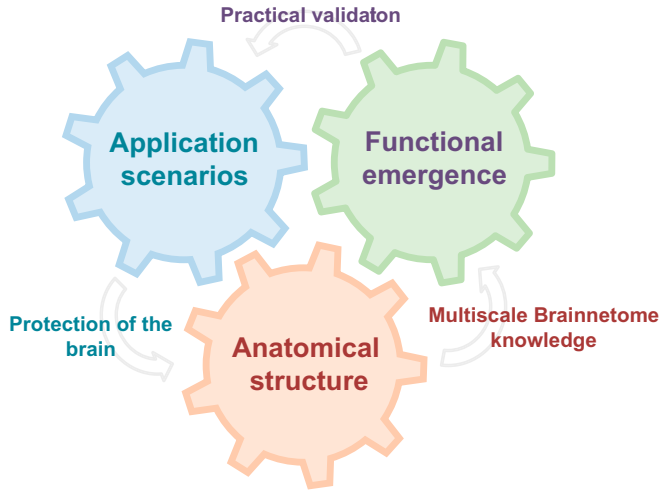

Fig. 4. A blueprint of the closed-loop DTB.

brainnetome knowledge accumulated from anatomical structures, which is the structural backbone to digitally twin the brain, multiscale artificial or biophysical algorithms allow us to simulate the neural dynamics for underpinning the emergence of functions from the structural backbone. A wide spectrum of practical scenarios, such as psychopathology discovery and psychoactive drug tests, are essential to validate the DTB and further help to understand and protect our brain. These, in turn, will generate feedback to incorporate multiscale information from the structural scaffold, thus enabling a more realistic simulation of brain functions. Altogether, the interactional relationship between these cores makes a closed-loop DTB to dynamically evolve according to the unceasingly accumulated brainnetome knowledge, the newly developed algorithms, and application scenarios that continue to emerge. The establishment of such a closed-loop DTB following the blueprint requires the collaborative efforts of researchers from different scientific backgrounds. Previous international projects and initiatives, including the Blue Brain Project [149], the Human Brain Project [150], the BRAIN Initiative [151], and the Neurotwin Initiative [152], have been launched and have made fruitful achievements, beginning the step toward development of the DTB. This type of collaboration will hopefully accelerate the realization of our DTB, which will bridge the gap between biological and artificial intelligence and foster the development of artificial general intelligence and precision medicine.

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